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Haemophilus influenzae type b conjugate vaccine for preventing pneumonia in infants hospitalized for bronchiolitis: A case—control study

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Summary
Background: *Haemophilus influenzae* type b (Hib) conjugate vaccine reduces the risk of pneumonia in infants.
Objective: To determine the effect of Hib conjugate vaccine (HibCV) on the prevention of pneumonia as a complication among infants hospitalized for bronchiolitis.
Methods: This record-based case—control study was conducted at The Children's Hospital "Dr. Ovidio Aliaga U" in La Paz, Bolivia during 2003 and 2004. Cases were infants hospitalized for bronchiolitis under 1 year of age who developed radiological pneumonia during hospitalization. Controls were patients who had good clinical progress without the use of antibiotics. Pneumonia was defined by alveolar consolidation on chest X-ray that justified the use of antibiotics.
Results: Eighty patients were studied (16 cases and 64 controls). Their median age was 4.5 months. Demographic and clinical features were similar in both groups, except for a higher proportion of vomiting (56.3% vs. 28.1%; $p < 0.05$) in the case group. The percentage of unvaccinated infants was significantly higher in cases (68.8% vs. 26.6%; $p < 0.05$) and the length of hospital stay longer (8.5 ± 5.4 vs. 3.1 ± 2.2 days; $p < 0.05$). There was a strong association between unvaccinated infants and the occurrence of pneumonia as a complication (odds ratio 6.1, 95% confidence interval 1.8—20.1; $p < 0.01$).
Conclusions: Unvaccinated infants admitted for bronchiolitis have a higher risk of radiologically confirmed pneumonia. Larger studies are needed to validate these results and reconsider the burden of Hib infection among infants in less developed countries.

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Introduction

Pneumonia is the leading killer of children and infants worldwide.[1] *Haemophilus influenzae* type b (Hib) is an important cause of pneumonia in children, responsible for approximately 20–25% of severe pneumonia cases.[1,2] Hib infection is rare before 4 months of age, owing to passive protection by transplacentally acquired antibodies, and again after 4 years of age, by which time natural immunity has developed.[3]

Bronchiolitis is the most common lower respiratory infection in infants under 1 year and is usually caused by a viral agent, predominantly respiratory syncytial virus (RSV).[4] Several recent studies in the USA, where Hib vaccination rates are high, have reported low rates of serious bacterial infections including pneumonia in non-severe cases of bronchiolitis and/or RSV infections (0–3.7%).[4–6] However, no similar data are available in the medical literature from developing countries. This is likely because Hib is often underappreciated as a cause of severe bacterial pneumonia due to the lack of adequate testing facilities and resources for laboratory diagnosis. Consequently, the true burden of Hib disease is not known.[7,8] In Bolivia, 79% of infants under 1 year of age were immunized against Hib in 2003,[9] but data on nasopharyngeal Hib carriage in this population were not collected.

Case–control studies and vaccine trials have provided evidence of the effectiveness of Hib conjugate vaccine (HibCV) for the prevention of pneumonia and have helped to estimate the burden of bacterial pneumonia.[10] Hib vaccination has been shown to reduce the risk of radiologically confirmed pneumonia in community-based studies.[10] However, no previous studies have reported benefits in infants hospitalized for bronchiolitis. The objective of this study was to determine the effect of HibCV for preventing pneumonia in infants under 12 months of age hospitalized for bronchiolitis.

Methods

This case–control study included infants aged 2–11 months admitted to the Respiratory Medicine Unit of The Children's Hospital "Dr. Ovidio Aliaga U" in La Paz, Bolivia for bronchiolitis during 2003 and 2004. Cases were infants under 1 year of age who developed radiographically confirmed pneumonia during hospitalization and required the use of antibiotics. Controls were patients who had good clinical progress during hospitalization without the use of antibiotics. Infants were immunized using a diphtheria–tetanus–pertussis–hepatitis B/*Haemophilus influenzae* type b (DTPw–HB/Hib) combination vaccine (Tritanrix® HB + Hiberix®, GlaxoSmithKline) at 2, 4, and 6 months of age in accordance with the national immunization schedule. Patients who received this vaccine according to their age were classified as vaccinated infants independently of the number of doses. None of the selected infants had received the pneumococcal polysaccharide vaccine (PPV). Clinical diagnosis of bronchiolitis was established by general pediatricians and senior pediatric residents who admitted the patients through the Emergency Department based on history and physical examination. All admitted patients had World Health Organization (WHO) criteria for severe respiratory infection based mainly on respiratory rate.[11] A chest radiograph was performed in all patients on admission, which was used as evidence that the patient did not have pneumonia at admission. Pneumonia as a complication during hospitalization was defined radiographically by an alveolar consolidation (a dense or fluffy opacity that occupies a portion or whole of a lobe or of the entire lung that may or may not contain air-bronchograms) on chest X-ray interpreted by attending physicians following standardized parameters[12] and that justified the use of antibiotics. The need for a second chest radiograph and the use of antibiotics during hospitalization was exclusively based on the physician's assessment and the patient's clinical progress. Vaccination status did not influence clinical decisions because physicians were unaware of the hypothesis under evaluation. All data collection was retrospective, and every patient's record was completely reviewed from admission to discharge through the use of a structured form. Information on clinical findings, laboratory results, interventions, and outcomes was registered and transferred into a database for statistical analysis.

The sample size was calculated considering a 21% expected frequency of unvaccinated infants in the control group,[8] a risk six times greater among unvaccinated infants than vaccinated infants for developing pneumonia, and statistical power of 80%, confidence level of 95%, and 4:1 ratio between control/case groups. Descriptive statistics (mean, median, standard deviation, and percent) were used to describe study variables. Continuous variables were compared using both the *t*-test and Mann–Whitney test for normal and skewed distributions, respectively. Proportions were compared by Chi-square statistics. The risk was estimated by odds ratio (OR) and confidence intervals (CI) using contingency tables. Finally, to assess the independent effect of immunization status on the risk of radiological pneumonia, we performed a multiple logistic regression analysis with radiographic pneumonia as the outcome variable and statistically significant differences found as predictor variables. All data were analyzed with SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The study sample consisted of 80 infants (64 controls and 16 cases) aged <1 year who were hospitalized for bronchiolitis as a principal diagnosis over a 24-month period. Clinical and demographic characteristics of these patients are shown in Table 1. The median age of admitted patients was 4.5 months. The time of illness before admission was significantly longer among infants who developed pneumonia as a complication (6.8 ± 5.0 vs. 4.4 ± 3.5 days; $p < 0.05$). Vomiting as a symptom occurred more frequently among cases than controls (56.3% vs. 28.1%; $p < 0.05$). The proportion of exclusively breastfed infants was similar in both groups. The white blood cell (WBC) count was slightly increased in cases (11.5 ± 3.8 vs. $8.4 \pm 3.1 \times 10^9$/l ; $p < 0.05$), and the relative lymphocyte count lower compared to controls.

The proportion of unvaccinated infants was significantly higher in cases than in controls (68.8% vs. 26.6%; $p < 0.05$). There was a strong association between not having received HibCV and the occurrence of pneumonia in infants with bronchiolitis (OR 6.1, 95% CI 1.8–20.1; $p < 0.01$). In the multiple logistic regression analysis including immunization status, time of illness before admission >96 h, and WBC count $>15 \times 10^9$/l, the adjusted OR (AOR) for estimating

Table 1 Clinical and sociodemographic characteristics of infants admitted for bronchiolitis

	Cases ($N = 16$)	Controls ($N = 64$)	p-Value
Age (months)[a]	5.7 ± 3.2	5.0 ± 2.5	0.58
Gender, female/male (%)	31.2/68.8	56.3/43.7	0.07
Exclusively breastfed infants (%)	50	62.5	0.36
History of prematurity (<38 weeks) (%)	6.3	9.4	0.59
Unvaccinated infants (%)	68.8	26.6	<0.05
Clinical features			
Time of illness before admission (days)[a]	6.8 ± 5.0	4.4 ± 3.5	<0.05
Cough (%)	87.5	96.9	0.12
Wheezing (%)	50.0	73.4	0.07
Increased work of breathing (%)	68.8	45.3	0.09
Crackles (%)	31.3	14.1	0.11
Fever at admission (%)	31.3	18.8	0.27
Vomiting (%)	56.3	28.1	<0.05
Lab tests			
White blood cell count ($\times 10^9$/l)[a]	11.5 ± 3.8	8.4 ± 3.1	<0.05
Relative lymphocyte count (%)[a]	46.7 ± 11.7	58.1 ± 16.5	<0.05
Progress			
Length of hospital stay (days)[a]	8.5 ± 5.4	3.1 ± 2.2	<0.05

[a] Values expressed as mean $\pm$ standard deviation.

the independent effect of immunization status on the risk of radiological pneumonia was 5.88 (95% CI 1.59—21.64; $p < 0.05$).

Efforts to identify viral etiology through indirect fluorescent antibody detection of nasopharyngeal aspirates were made in 23 patients. Viral testing was positive for RSV in nine infants (39%). Two of these infants who had confirmed RSV infection developed radiologically confirmed pneumonia and required antimicrobial therapy. Blood cultures were not performed in any case.

Discussion

In this case—control study that includes a sample of infants hospitalized for bronchiolitis, the higher prevalence of radiologically confirmed pneumonia found in unvaccinated infants suggests that Hib infection could have a significant role in bronchiolitis complications. To our knowledge, this is the first study in the medical literature that reports the risk of pneumonia in bronchiolitis considering vaccination status.

With the availability of effective vaccines against one of the two leading bacterial pathogens causing childhood pneumonia in developing countries, the need for standardized methods to collect data on the pneumonia disease burden and the proportion of the burden preventable by vaccines has become critical.[13] Frustration associated with the lack of refined clinical and laboratory diagnostic tools to define the burden of vaccine-preventable diseases has prompted investigators to use vaccines as a 'probe'.[14] Previous studies in developing countries support the concept that vaccines can be used as 'probes' to unmask the burden of diseases that may be missed by culture-based methods.[9] Thus, vaccine trials have helped to estimate the burden of vaccine-preventable disease by providing a measurable 'vaccine effect', which is the difference in incidence or prevalence of a condition between vaccinated and unvaccinated groups.[10,15] Although the present retrospective case—control study has several well-known limitations,[14] it is based on the 'vaccine trial' concept described above.

The Hib vaccine is safe and effective in preventing invasive Hib disease. In a recent Cochrane systematic review, the findings of randomized controlled trials that evaluated the effect of conjugate vaccines for preventing *H. influenzae* type b infections suggest a reduction between 46% and 93% in Hib invasive disease. Furthermore, authors found no evidence that the effectiveness of the vaccine was modified by the type of conjugate vaccine, the number of doses given (two, three, or four), or age at first vaccination (2 months, 42 to 90 days, 3 months).[2] In this study we did not specifically evaluate these variables, but it is evident that even one dose could be beneficial for preventing pneumonia in infants hospitalized for bronchiolitis.

Classically, conventional diagnosis of pneumonia consists of two stages: first, determining the syndrome by history, clinical examination, and chest radiography; and second, determining the etiology by microbiological, serological, and molecular tests.[16] In this study, the use of a radiographic definition of pneumonia deserves particular consideration. First, in contrast to the situation in industrialized countries, the majority of Hib disease in developing countries manifests as pneumonia. Unfortunately, it is more difficult to establish a causative agent for pneumonia than for meningitis.[9] To identify a case of Hib pneumonia with certainty, it is necessary to identify the Hib organism from culturing blood, lung aspirate, or pleural fluid.[15] Although blood culture offers an excellent opportunity for the etiological diagnosis of bacterial pneumonia, it is only useful in bacteremic pneumonia. The yield from blood culture in patients with pneumonia has ranged from 10% to 30%.[14] A diagnostic lung tap may provide valuable information for the etiology of non-bacteremic pneumonia, but does not provide complete data.[14] Second, the diagnosis of bacterial pneumonia in the face

of bronchiolitis or RSV infection is extremely difficult. Fever, pulmonary infiltrates, positive tracheal aspirate cultures, and elevated peripheral WBC counts are common findings in respiratory infection and cannot be used to distinguish bacterial from viral causation.[17] To be effective in the developing world, a diagnostic test must be rapid, simple to execute, and inexpensive and one has not yet been developed.[16]

Radiological findings are commonly accepted as the gold standard for defining pneumonia.[14] The presence of significant alveolar consolidation is considered by most authorities to be the most specific radiographic predictor of bacterial pneumonia.[12,13] In addition, previous studies had shown that there is reasonable inter-observer agreement on the presence of alveolar consolidation.[18,19] Although current evidence does not support routine radiography in children with bronchiolitis, this resource may be useful when the hospitalized infant does not improve at the expected rate, if the severity of disease requires further evaluation, or if another diagnosis is suspected.[4] It has been suggested that bacterial pneumonia in infants with bronchiolitis without consolidation is unusual.[20]

The lack of confirmatory laboratory test results to diagnose bronchiolitis is also a limitation in this study. However, the clinical utility of diagnostic testing in infants with suspected bronchiolitis is not well supported by evidence.[21] In addition, recent American Academy of Pediatrics recommendations for the diagnosis and management of bronchiolitis suggest that bronchiolitis diagnosis should be based on patient history and physical examination.[4] Recent clinical reviews on bronchiolitis confirm that infants younger than 6 months of age are at the highest risk of clinically significant disease and that more than half of affected children are aged between 2 and 7 months.[22] This description correlates with the demographic characteristics of infants studied in this report. Additionally, cough and wheezing associated with increased work of breathing, the most common clinical features of bronchiolitis,[4] were present in the majority of patients included. Beside the low proportion of prematurity found in this study, no other risk factors for severe disease, such as age less than 12 weeks, underlying cardiopulmonary disease or immunodeficiency, were identified.

Previous studies have reported that breastfeeding decreases the risk of lower respiratory tract disease (LRTD). However, the proportion of breastfed infants found in this study was comparable in both cases and controls. This variable was not shown to increase the risk for developing pneumonia as a complication in infants hospitalized for bronchiolitis. A meta-analysis of the relationship of breastfeeding and hospitalization for LRTD in early infancy that examined 33 studies showed a protective association between breastfeeding and the risk of hospitalization for LRTD.[23] In addition, other studies have shown that breast milk provides immunity and neutralizing factors against RSV, decreasing hospitalization related to RSV infection and other lower respiratory tract infections.[4] Furthermore, it has been suggested that breastfed compared with formula-fed infants responded with higher or equivalent antibody levels to a series of three doses of conjugate Hib vaccine, leading to speculation that breastfeeding, or some components of breast milk, may enhance the active immune response in the first year of life.[24] Conversely, a recent Australian report did not show this effect among breastfed infants.[25] The authors suggest that additional studies are needed to determine the benefits of breast milk on infant Hib immunization responses.

Since we performed a retrospective analysis of registry data, we cannot establish cause and effect. However, the association found is strong and consistent with prior community-based studies. Based on these findings, it would be reasonable to have a low threshold for starting antibiotic therapy in unvaccinated infants with bronchiolitis who have physical or radiological features suggesting bacterial pneumonia. The antibiotic coverage under these circumstances should include agents such as third-generation cephalosporins to treat a possible Hib infection. If these results are validated in further studies, the incorporation of this risk factor in clinical practice for the prediction of a secondary bacterial infection as a complication in bronchiolitis could help to prevent morbidity and mortality from an untreated bacterial infectious disease in an initially suspected viral infection. The development of better tools to determine the microbiological diagnosis of pneumonia is also critical for additional analysis.

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